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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/421,778	10/19/99	FULLER J	APF-30.20

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EXAMINER	
NGUYEN, V	

ART UNIT	PAPER NUMBER
1632	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/421,778	FULLER, JAMES T.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *9,10,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-17 and 20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-8, 11-17, 20-27, drawn to a method of obtaining expression in mammalian cells of a polypeptide of interest, wherein the polypeptide is an antigen of a viral, bacterial, parasite or fungal pathogen, coated particles comprise a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence encoding the same antigen, a particle accelerating device for delivering the same coated particles, an isolated minimal promoter sequence and a nucleic acid construct comprising the same, classified in class 514, subclass 44.

II. Claims 1-7, 9, 11-16, 18, 20-27, drawn to a method of obtaining expression in mammalian cells of a polypeptide of interest, wherein the polypeptide is a tumor specific antigen or an antigen associated with an autoimmune disease, coated particles comprise a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence encoding the same antigen, a particle accelerating device for delivering the same coated particles, an isolated minimal promoter sequence and a nucleic acid construct comprising the same, classified in class 514, subclass 44.

III. Claims 1-7, 10, 11-16, 19-27, drawn to a method of obtaining expression in mammalian cells of a polypeptide of interest, wherein the polypeptide is

an antigen comprises a B-cell epitope or a T-cell epitope, coated particles comprise a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence encoding the same antigen, a particle accelerating device for delivering the same coated particles, an isolated minimal promoter sequence and a nucleic acid construct comprising the same, classified in class 514, subclass 44.

The inventions are distinct, each from the other because of the following reasons:

Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: Groups I, II and III are directed to methods that are distinct in utilizing antigens of different chemical structures and functions and are not required one for the other. Invention I requires the antigen of a viral, bacterial, parasite or fungal pathogen, Invention II requires a tumor specific antigen or an antigen associated with an autoimmune disease, and Invention III requires an antigen comprising a B-cell epitope or a T-cell epitope.

Because these inventions are distinct for the reasons given above, restriction for examination purposes as indicated is proper.

During a telephone discussion with Attorney Thomas P. McCracken on August 28, 2000, a provisional election was made without traverse to prosecute the invention of group I. Affirmation of this election should be made by applicant in replying to this Office action.

Groups II and III are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being for nonelected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 8 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of obtaining expression in mammalian cells of a polypeptide of interest wherein the polypeptide is an antigen of a viral, bacterial, parasite or fungal pathogen and *in vivo* or autologous *ex vivo* methods of obtaining expression the same antigen in non-human mammalian cells, does not reasonably provide enablement for any and all *in vivo* or *ex vivo* methods of expressing any and all polypeptide of interest in any and all mammalian cells for the purposes of genetic therapy and nucleic acid immunization. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are drawn to a method of obtaining expression in mammalian cells of a polypeptide of interest, which method comprises transferring into said cells a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the polypeptide. Claim 5 is directed to the same method wherein the construct is delivered *ex vivo* into cells taken from a subject and the cells are reintroduced into the subject.

The specification discloses the construction of Hepatitis B surface antigen (HbsAg) expression cassettes driven by full-length or minimal promoter systems (with or without enhancer, respectively) derived from simian CMV, human CMV and pseudorabies virus (PRV). The DNA constructs were coated onto gold carrier particles and administered to Balb/c mice using a particle-mediated delivery technique. Analysis of anti-HbsAg antibodies in sera taken from vaccinated mice six weeks later, revealed that minimal promoter system gave a significant improvement in antibody titer over the fully enhanced promoter system.

The above evidence is noted and considered. However, the evidence can not be extrapolated to the instant claimed invention which when read in light of the specification, encompasses *in vivo* and *ex vivo* methods of obtaining expression in any and all mammalian cells of any and all polypeptide of interest for the elected invention for gene therapy and nucleic acid immunization purposes (see instant specification,

page 1, lines 14-15). Besides the stated purposes, it is unclear from the present application what other use that the claimed method would serve.

The specification is not enabled for such a broadly claimed invention. With regard to the gene therapy aspect encompassed by the instant claimed invention, at the effective filing date of the instant application the art of gene therapy is immature and highly unpredictable. In a meeting report on a workshop for gene therapy and translational cancer research (Clin. Cancer Res. 5:471-474, 1999), Dang et al. noted that further advancement in all fields including, gene delivery, gene expression, immune manipulation, and the development of molecular targets is needed to make gene therapy a reality. They further cited the findings of the Orkin-Motulsky Committee (commissioned by the NIH director) which found that human gene therapy is an immature science with limited understanding of gene regulation and disease models for preclinical studies (First paragraph, page 471). Dang et al. pointed out several factors limiting an effective human gene therapy, including, sub-optimal vectors, the lack of long term and stable gene expression, and most importantly the efficient gene delivery to target tissues (last paragraph, page 474).

The specification fails to provide sufficient guidance and examples demonstrating that aforementioned hurdles in gene therapy could be overcome. Although the minimal promoter system of the instant claimed invention yields a significantly improvement in antibody titer relative to the fully enhanced promoter system, there is no evidence indicating that the same minimal promoter system can provide a stable and sufficient expression levels of any and all polypeptide of interest to achieve therapeutic effects.

Current available gene delivery systems (both viral and non-viral vectors) have been reviewed by Wivel and Wilson (Methods of gene delivery, Hematol. Oncol. Clin. North Am. 12:483-501, 1998). In a summary, Wivel and Wilson stated that "One of the major challenges still confronting the field is the design of more efficient vectors. The gene delivery systems being used today will undoubtedly be seen as crude when compared with future developments. It is unlikely that there will ever be a universal vector, but rather there will be multiple vectors specifically designed for certain organ sites and certain diseases.....It will be necessary to do much more fundamental research in cell biology, virology, immunology, and pathophysiology before vectors can be significantly improved." (pages 498-499 in Summary section). The specification fails to provide any information regarding to the fate of delivered nucleic acid construct, the fraction of the nucleic acid construct taken up by the target cell population, the rate of nucleic acid construct being degraded *in vivo*, the stability of the protein/polypeptide produced, the compartmentalization of protein or polypeptide within the cell or its secretory fate. These factors differ dramatically based on the protein or polypeptide produced, and thus the desirable therapeutic effect being sought is not always predictable and can not be overcome by routine experimentation.

The breadth of the instant claims encompasses many routes of administering the nucleic acid construct, however, the specification does not provide any teaching regarding to the delivery of said nucleic acid construct to the intended target cell population. Vector targeting *in vivo* to desired cells continues to be unpredictable and inefficient. This is supported by numerous teachings in the art. As an example, Verma

& Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy, and the problems which are associated with each. They indicated clearly that about the effective filing date of the present application the resolution to vector targeting had not been achieved in the art (see the entire article). Verma & Somia discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that an efficient expression is not achieved (see page 239, and second and third columns of page 242). The instant specification fails to teach one of skilled in the art how to overcome the unpredictability for vector targeting such that an efficient transfer of the nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for a polypeptide of interest to desired cells or tissues is achieved by any mode of delivery as encompassed by the breadth of the claims.

The breadth of the broadest claim also encompasses an *ex vivo* approach for obtaining the expression of a polypeptide of interest in mammalian cells of a subject for gene therapy and nucleic acid immunization purposes. The specification fails to provide direction and examples showing that immune-mediated rejection of genetically modified allogeneic and xenogeneic cells can be suppressed or eliminated in order to obtain therapeutic effects. Moreover, the genetically modified cells in the claims also encompass genetically modified stem cells. At the effective filing date of the instant application, cell transplantation therapies with genetically altered cells to treat diseases or disorders are neither routine nor predictable. Regarding to the utilization of mesenchymal stem cells for human gene therapy, Gerson (Nature Med. 5:262-264,

1999) indicated many questions that need to be addressed, such as, "What is the minimum proportion of donor mesenchymal stem cells required to affect a long-lasting therapeutic response?", "Will transplantation of mesenchymal stem cells from a marrow harvest or from culture-expansion be sufficient to treat other diseases?", "Can culture-expanded mesenchymal stem cells substitute for fresh marrow allografts in the correction of genetic disorders of the mesenchyme?", "To which host tissues do infused mesenchymal stem cells home, proliferate and differentiate, and using which regulatory signals?", "Can mesenchymal stem cells be used effectively for gene transfer and gene deliver?", "Is systemic infusion optimal or is infusion into a target organ required?" (column 1, second paragraph, page 264). The specification does not provide any guidance in addressing these fundamental questions, and therefore it would have required undue experimentation for one skilled in the art to practice the claimed invention.

With regard to the nucleic acid immunization aspect encompassed by the instant claimed invention, the state of the art is new and unpredictable at the effective filing date of the present application. Chattergoon et al. (FASEB J. 11:753-763, 1997) stated that "Though DNA vaccines have shown promise in animal models and have raised hopes, the technology is considered an emerging technology" (column 1, paragraph 2, page 762) and "There is little evidence that the immune response induced by these vaccines will be completely protective against any human pathogen" (page 762, paragraph bridging columns 1-2). Specifically regarding to DNA immunization, it is recognized that the animal model should correlate to the disease conditions studied. It

is impossible to predict whether an untested antigen of an infectious pathogen will elicit a protective immune response in a given type of animal and the route of administration was recognized as being a critical parameter determining whether protective immunity is elicited. One skilled in the art would have also recognized that results observed in animal model system following testing of a DNA expression vector-based agent are not predictive of outcome or efficacy in applications in other species of animal or in humans, due to differences in anatomy, cell biology, genetics, and immunology between different types of animals and between the animal models and humans. This is supported by the teachings of McCluskie et al. (Mol. Med. 5:287-300, 1999) who stated that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors." (column 2, last paragraph, page 296). The instant specification fails to provide sufficient guidance or direction and examples demonstrating that the claimed method utilizing the disclosed nucleic acid construct is effective for nucleic acid immunization purpose in any and all mammalian subjects.

Accordingly, due to the lack of guidance and examples for the claimed method to be used effectively for gene therapy or nucleic acid immunization, the unpredictability and current state of the arts, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **us**- the broadly claimed invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 6 is drawn to a method of obtaining expression in mammalian cells of a polypeptide of interest of the elected invention, which method comprises transferring into said cells the same nucleic acid construct and wherein the subject is human.

The specification is not enabled for the instant claimed invention for reasons cited in the preceding rejection of claims 1-5, 7, 8 and 11-14.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 11-17 and 20-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and its dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is the expression of the polypeptide by the nucleic acid construct that is transferred into mammalian cells. Simply transferring said nucleic acid construct into mammalian cells does not necessarily results in the expression of the coding sequence for the polypeptide. Clarification is requested.

In claims 1, 15, 24, 25 and their dependent claims, the term "minimal promoter" is vague on the basis of its definition given in the instant specification on page 10, lines 7-8. It appears that it reads on any promoter. Therefore, the term renders the claims indefinite since the metes and bounds of the claims can not be clearly determined. Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 12-14 and 24-27 are rejected under 35 U.S.C. 102(a) as being anticipated by A-Mohammadi & Hawkins (Gene therapy 5:76-84, 1998).

The claims are drawn to a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence, a vector comprising the same nucleic acid construct, a purified and isolated minimal promoter sequene, and a method of obtaining expression in mammalian cells of a polypeptide of interest using the same. Claims 13 and 14 are drawn to the same method wherein the minimal promoter sequence consists essentially of a hCMV immediate early promoter sequence, a pseudorabies virus early promoter sequence, a simian cytomegalovirus immediate early promoter sequence or a functional variant thereof, and wherein the minimal promoter

sequence consists essentially of the sequence spanning positions 0 to –118 of the hCMV immediate early promoter region or a functional variant of the said spanning sequence, respectively.

A-Mohammadi & Hawkins disclosed the construction and analysis of tetracycline-regulatable plasmid vectors comprising a bidirectional minimal promoter of $pCMV^{*-1}$ operably linked to coding sequences (See Fig. 1). An enhancerless positive feedback regulatory vector construct pSialV transcribing both the tetracycline-controlled transactivator (tTA) and mGM-CSF from a modified tTA-responsive bidirectional promoter demonstrated over 200 fold gene regulation in HeLa cells (See Fig. 5). The maximal transcriptional activity of pSialV was comparable to that of intact CMV IE promoter and its basal activity was repressed to the leakiness of the tetracycline-responsive promoter in response to tetracycline. Since a functional variant encompasses truncated functional versions of the minimal promoter sequence and functional fragments of a native promoter sequence (see instant specification on page 10, lines 27-29 and page 11, lines 1-2), the teachings of A-Mohammadi & Hawkins meet all the required elements in the claims. Therefore, the reference anticipates the claimed invention.

Claims 1, 12-14 and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Hofmann et al. (Proc. Natl. Acad. Sci. 93:5185-5190, 1996).

Hofmann et al. disclosed a recombinant retroviral vector construct (SIN-RetroTet vector) containing an autoregulatory cassette comprising a heptamerized tet operator

sequence $(TetO)_7$ fused to the human CMV immediate early minimal promoter $P_{hCMV*-1}$ (See Fig. 1). Analysis of transduced C57BL/6 primary myoblasts revealed that the construct yields low basal levels of gene expression and induction of one to two orders of magnitude. In this instant, beta-galactosidase is the polypeptide of interest. With respect to the definition of a functional variant mentioned above, the disclosure of Hofmann et al fulfilled all required elements in the claims. Thus, the reference anticipates the instant claimed invention.

Claims 1-4, 7, 8, 11-17, 20-23 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Lai et al. (DNA Cell Biol. 14:643-651, 1995).

The claims are directed to a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence, particles coated with the same nucleic acid sequence wherein the coding sequence encoding an antigen (preferably an antigen of a viral, bacterial, parasite or fungal pathogen), a particle accelerating device loaded with the same coated particles, and a method for obtaining expression in mammalian cells of a polypeptide of interest, preferably an antigen, using the same nucleic acid and coated particles.

Lai et al. disclosed a vaccine DNA construct comprising a DNA fragment of *Mycoplasma pulmonis* encoding a protein recognized by a protective monoclonal antibody, under the control of the CMV immediate early promoter. Gold particles were coated with the vaccine DNA construct, and delivered directly into the skin of mice using a helium-driven, hand-held gene gun (column 2, first paragraph, page 645). Both

humoral and cellular immunity were induced, and vaccinated mice were protected from infection upon challenges with *Mycoplasma pulmonis*. Due to the open language of the term "comprising" in the claims, the claimed nucleic acid construct encompasses enhancer elements in addition to a minimal promoter sequence. Therefore, the teachings of Lai et al. met all essential components of the instant claims, and the reference anticipates the claimed invention.

Claims 1, 5, 7, 8 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Laube et al. (Hum. Gen.Ther. 5:853-862, 1994).

The claims are drawn to a method of obtaining expression in mammalian cells of a polypeptide of interest, and wherein the method comprises *ex vivo* deliverance into cells taken from a subject a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the polypeptide, and the cells are reintroduced into the subject. The claims are also directed to a method of obtaining expression in mammalian cells of a polypeptide of interest, wherein the polypeptide is an antigen, preferably the antigen of a viral, bacterial, parasite or fungal pathogen, and wherein the nucleic acid construct is a DNA construct.

Laube et al. disclosed *ex vivo* transduction of autologous non-human primate rhesus monkey fibroblasts derived from skin biopsies with a retroviral vector encoding HIV-1 IIIB ENV/REV proteins, followed by the readministration of retroviral vector-transduced fibroblasts into the animals to generate cytotoxic T lymphocyte and antibody responses (See abstract). Because of the term "comprising" in the claims as already

discussed above, the teachings of Laube et al. met all the elements recited in the claims, and thus the reference anticipates the claimed invention.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, J.D., may be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Quang Nguyen, Ph.D.
Examiner, AU 1632

Karen M. Hauda

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